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Mortality and cancer incidence in perfluorooctanesulfonyl fluoride production workers

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Abstract

Background: Exposure to per- and polyfluoroalkyl substances (PFAS) has been associated with several health outcomes, though few occupationally-exposed populations have been studied. We evaluated mortality and cancer incidence in a cohort of perfluorooctanesulfonyl fluoride-based specialty chemical manufacturing workers.

Methods: The cohort included any employee who ever worked at the facility from 1961 to 2010 ($N = 4045$), with a primary interest in those who had 365 cumulative days of employment ($N = 2659$). Vital status and mortality records were obtained through 2014 and the cohort was linked to state cancer registries to obtain incident cancer cases from 1995 to 2014. Cumulative exposure was derived from a comprehensive exposure reconstruction that estimated job-specific perfluorooctanesulfonate (PFOS)-equivalents (mg/m^3) exposure. Overall and exposure-specific standardized mortality ratios (SMR) were estimated in reference to the US population. Hazard ratios (HRs) and 95% confidence interval (CI) for cumulative PFOS-equivalent exposure (log_2 transformed) were estimated within the cohort for specific causes of death and incident cancers using a time-dependent Cox model.

Results: Death rates were lower than expected except for cerebrovascular disease (SMR = 2.42, 95% CI = 1.25–4.22) and bladder cancer (SMR = 3.91, 95% CI = 1.07–10.02) in the highest exposure quartile. Within the cohort, the incidence of bladder, colorectal, and pancreatic cancer were positively associated with exposure, however except for lung cancer (HR = 1.05, 95% CI = 1.00–1.11) the CIs did not exclude an HR of 1.

Conclusions: This study provides some evidence that occupational exposure to PFOS is associated with bladder and lung cancers and with cerebrovascular disease.

KEYWORDS
cancer incidence, mortality, per- and polyfluoroalkyl substances, perfluorooctanesulfonate, PFAS, PFOS

Work was performed at the University of Minnesota.

1 | INTRODUCTION

Per-and polyfluoroalkyl substances (PFAS) are specialty chemicals that have garnered considerable attention due to widespread exposure, persistence of the chemicals, and concerns of potential health effects.[1] The International Agency for Research on Cancer (IARC) classified perfluorooctanoic acid (PFOA) as possibly carcinogenic to humans (2B)[2] and IARC Workshop 135 scheduled for November 2023 has been charged to reassess the carcinogenicity for both PFOA and perfluorooctanesulfonate (PFOS).[3] The United States Environmental Protection Agency (USEPA) in its drinking water advisories cited suggestive evidence that both PFOA and PFOS are carcinogenic, but a new draft assessment by USEPA indicates probable carcinogenicity.[4,5]

Human PFAS exposure through various environmental media is ubiquitous and results in widespread low-level PFAS body burdens.[1] Some populations have experienced higher community exposures mostly through contaminated drinking water supplies. The extensive use of PFAS in industrial applications and consumer products gave rise to potential exposure in a wide range of occupations.[6] The level of PFAS in serum of exposed workers is notably higher than that of the general population in which serum levels have declined approximately 70%–80% (NHANES) between 2000 and 2018 for PFOA and PFOS and somewhat lower percentages for perfluorohexanesulfonate (PFHxS) and perfluorononanoic acid.[7] Exposure to workers at the sites where PFAS are manufactured is often orders of magnitude above other lesser exposed workers.[8] Some evidence of health effects, including kidney cancer,[9] bladder cancer,[10] prostate cancer, diabetes, and cerebrovascular disease,[11] has been reported in these highly exposed PFAS manufacturing workers, but there is little consistency between the occupational studies.

The 3M facility in Decatur, Alabama, was a major production site of perfluorooctanesulfonyl fluoride (POSF, $C_8F_{17}SO_2F$)-based specialty chemicals from 1960 until production was phased out in 2002. POSF, which can degrade or be metabolized to PFOS, was the primary exposure in this population. Before 3M Company's announced phase-out of perfluorooctanyl chemistry in 2000, employees of the Decatur site had substantially higher PFOS and PFOA serum concentrations than the general population with their reported geometric mean serum concentrations of 941 ng/mL for PFOS and 889 ng/mL for PFOA[12,13] compared to 30.4 and 5.2 ng/mL in the general population as reported by the NHANES in 1999–2000.[7]

An excess in bladder cancer mortality in the Decatur workforce was previously observed based on three deaths.[10] Although a subsequent survey conducted to identify nonfatal bladder cancer cases through self-report, in addition to fatal bladder cancers, offered little support for an association with PFOS, the limited study size prohibited a conclusive exposure-response analysis.[14] The ongoing concern about potential PFAS-related health effects, and particularly increased cancer risk, warranted additional investigations of highly exposed worker cohorts. We updated the mortality analysis of the Decatur workforce, added a registry-based study of cancer incidence, and developed a more specific exposure model.

2 | METHODS

2.1 | Study population

POSF-based chemicals were produced at the Decatur facility from 1961 through 2002. Following the phase-out of POSF-based production, the buildings housing the electrochemical fluorination cells were dismantled and all other areas of the plant related to production were cleaned by the end of 2010. This cohort includes all employees who ever worked at the plant from 1961 through 2010. Consistent with our previously published work, the subcohort of primary interest was employees who had accumulated at least 365 days of employment ($N = 2659$). Employees with shorter durations of employment include summer interns who may not represent the population from which the main cohort came. For completeness, we also present the results of all potential cohort members ($N = 4045$).

2.2 | Site description

The 3M Decatur manufacturing site consists of two plants: Specialty Film (film plant) and Specialty Materials (chemical plant). Both plants began operations in the early 1960s. PFASs were not significantly used or produced in the film plant. PFOS, PFHxS, PFOA, and related materials were phased out of the chemical plant operations in the early 2000s. The three major product groups in the chemical plant were protective chemicals (e.g., carpets, textiles, paper), performance chemicals (e.g., heat transfer fluids, degreasing), and fluoroelastomers (e.g., gasket seals, bearing coatings). More than 1000 different processes, of which 700 were PFAS-related processes, were operated in the chemical plant, with the majority as batch processes with varying manufacturing frequencies over time. Raw materials and intermediates for each product group often flowed through different production buildings before packaging and shipment.

POSF was the major building block manufactured and used as the precursor to the manufacture of products which included a variety of perfluorinated amides, alcohols, acrylates, and other PFAS polymers produced as protective and performance chemicals. POSF was manufactured by reacting octyl mercaptan with chlorine, followed by a halogen exchange to produce octanesulfonyl fluoride (cell feed) in the Primary Product Building (Supporting Information S1: Figure S1). This cell feed was sent to the Electrochemical Cell Buildings to produce POSF, for the vast majority of all downstream PFASs produced in the primary and secondary product buildings.

POSF-based compounds were a small portion of the materials found in the majority of fluoroelastomer products produced in the reactor buildings, secondary product and workup building, and compounding building. The primary chemicals used in manufacturing fluoroelastomers were fluorinated alkanes and alkene gases. The chemical plant's main office areas, warehouse, and quality control laboratories were in one large building. Other buildings included the boilerhouse, maintenance and stockroom, and the site wastewater treatment plant.

2.3 | Exposure assessment

Previous studies of the Decatur workforce relied on a simple job exposure matrix that classified jobs as having no, low, and high POSF workplace exposure with a relative exposure weighting scale as a secondary exposure metric.[10,14,15] For this study, a comprehensive exposure reconstruction was developed to estimate time-weighted average (TWA) airborne exposure to seven target POSF-based chemicals resulting in an exposure metric of total PFOS-equivalents (mg/m^3). Exposure to other PFAS, for example, PFOA, did occur at the Decatur site, but were primarily a by-product of the POSF manufacturing process and thus considered a residual exposure without sufficient data to quantify the exposure. The objective of the exposure assessment was to assign each cohort member an annual cumulative metric of exposure that accurately represents the exposure experience of the entire cohort. To achieve this objective, we created a job-task-based exposure data matrix for TWA inhalation exposure incorporating time-variable production measurements. Specific tasks handling certain materials are the primary determinants of exposure for any given worker or group. For a department-specific job title, there could be groups or teams within the job title that perform very different tasks or handle different materials leading to the potential for exposure misclassification. A worker group handling a high concentration material, for even a short-term task, could have exposure levels much higher than other workers in the same department, making the use of only job title or department name a less accurate exposure metric. We therefore constructed time-specific exposure groups, rather than rely solely on job title and department, to obtain a time-dependent cumulative exposure for each worker in the plant. The following provides more detail to this procedure.

Exposure data systems were accessed to obtain task-specific personal exposure data. Comprehensive documentation of job tasks in production standards was available and interpreted by production engineers with direct experience across the majority of timeframes in the study. Batch production operations, like those in the chemical plant, often utilize task-based exposure assessment methods which allow for better evaluation of exposure controls, sources, personal protective equipment, and work practice or administrative controls.[16] Available air sampling data included details about the process, materials handled, exposure controls, and tasks being performed. This detailed basic characterization allowed sampling data to be effectively leveraged across similar tasks handling the same or similar materials.

This exposure-matrix approach using cumulative exposure is defined as the average exposure for each department-job-year combination and the time individuals or groups spend in each. The process of creating exposure groups or similar exposure groups (SEGs) has been well described in the American Industrial Hygiene Association (AIHA) report, which details how basic characterization, exposure assessment data, and task information can be used to retrospectively construct department-job-year combinations.[16]

To construct the initial exposure groups, we evaluated: (1) All relevant information on building layouts, ventilation systems, crew allocations, material compositions, production groupings, process flows, equipment, job titles, exposure controls and tasks; and (2) All job title and department information for employees to create a standardized list. We then engaged an extended network of 80 individuals knowledgeable in historical plant operations, including production, supervision, maintenance, engineering and human resources, to support all aspects of the exposure reconstruction. Numerous interviews of these employees and record reviews were led by a former plant production operations manager and two industrial hygienists knowledgeable of the site operations. A total of 2583 different job titles were extracted from computerized work history records to create the initial exposure groups.

For each initial exposure group, we developed process- and job-based exposure time estimates for exposure significant tasks (tasks that resulted in exposure to POSF-based processes), time spent in production areas not directly exposed, and time working out-of-production areas with minimal exposure. Applicable industrial hygiene monitoring data were then used to calculate exposure group annual TWA for each target PFAS across all processes and nonproduction jobs.

Determination of the total number of exposure groups was an iterative process that involved production data, maintenance operations, materials, and process chemistry, along with exposure significant tasks, site, and building or production changes over time. As exposure groups were established and refined with additional information, exposure significant tasks with exposure assessment data were reviewed and evaluated for the seven target chemicals of interest: perfluorooctane sulfonate (Na-PFOS or PFOS), N-methyl perfluorooctane sulfonamidoethanol (MeFOSE), N-ethyl perfluorooctane sulfonamidoethanol (EtFOSE), N-methyl perfluorooctane sulfonamide (MeFOSA), N-ethyl perfluorooctane sulfonamide (EtFOSA), and N-methyl perfluorooctane sulfonamidoethyl acrylate (MeFOSAC) (Figure 1). These chemicals were selected because they had a potential to hydrolyze into PFOS within the human body ultimately; therefore, a metabolism hydrolyzation factor (percent hydrolyzed to PFOS) was estimated for each of the seven chemicals based on available toxicological evidence[17] and applied as part of the exposure matrix.

Exposure monitoring data for each chemical included short-term and long-term personal air sampling measurements, area samples with task information, area samples without task information, and source and outdoor area monitoring. For each exposure group, the applicable sampling data were used to construct the TWA calculations based on the time (1) performing exposure tasks across the product groupings, (2) working in the production area but not performing exposure tasks, and (3) working outside relevant production areas and operations. Air sampling data for the seven chemicals were not available before 1978. Between 1978 and 1990 sampling data were stored in hard copy files which were converted into electronic spreadsheets records. After 1990 and up to 2010 sampling data were stored in electronic databases where the information could be extracted and assembled into spreadsheets for constructing exposure groups. A total of 1705 chemical exposure data points were utilized across all the exposure groups (Supporting Information S1: Table S1). The final exposure estimates based on these data were applied across all years.

Presented in Supporting Information S1: Table S2 are the 72 exposure groups that were defined in this study by timeframe listed and the "Total PFOS-Equivalent" TWA (mg/m^3) normalized on an annual

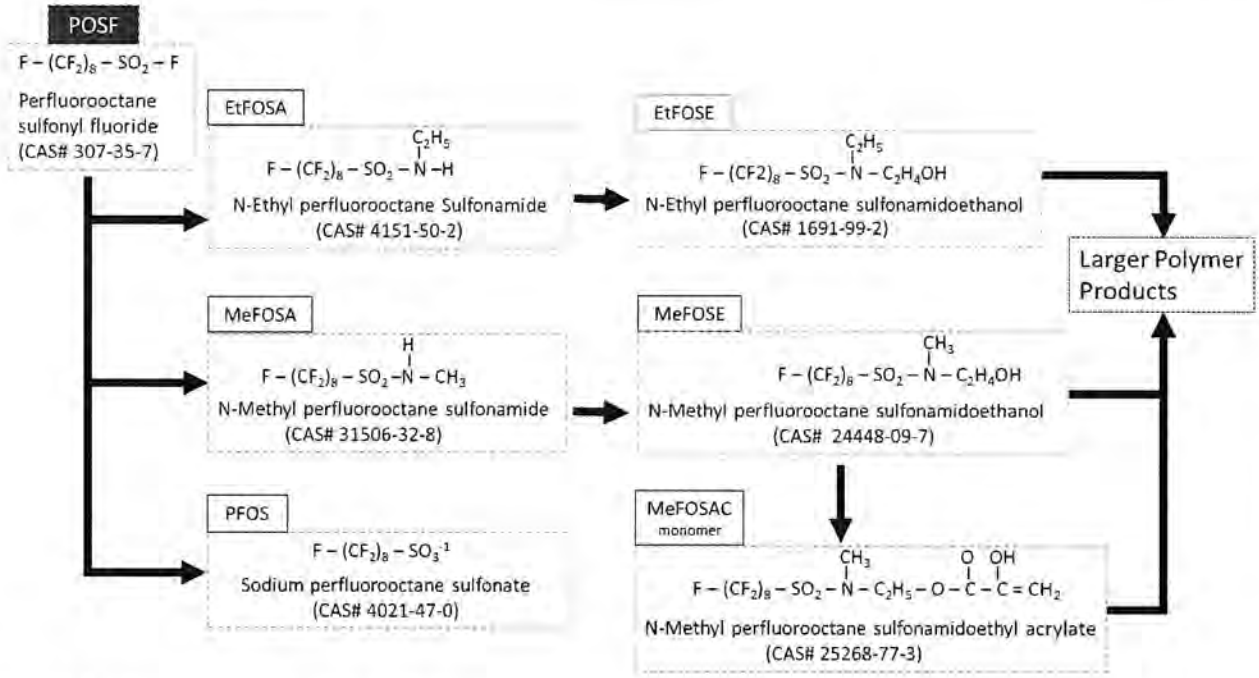

FIGURE 1 Chemistry tree for primary POSF-based production at Decatur site.

basis. A description of an exposure group may be represented by different timeframes (e.g., see exposure groups 2–4). The range of "Total PFOS-Equivalent" TWAs for these 72 exposure groups went from 0.0001 mg/m^3 (exposure group 70) to 1.3 mg/m^3 (exposure groups 28 and 29). The 72 exposure groups were then individually considered and applied for every job/department record change that occurred in each employee's work history between 1960 and 2010. A total of 35,442 job exposure group were decisions made among the 4045 Decatur employee's work history regardless of their time worked, and 31,116 job exposure group decisions were made for those 2659 Decatur employees who worked 1 year or longer. This amounted to an average of 8+ exposure group changes per individual, whether the entire time worked or the time worked for 1 year or longer. In either situation, the cumulative exposure for any individual was calculated as the sum of the amount of time worked for each exposure group in this person's Decatur history.

To illustrate the construction of the exposure matrix, Exposure Group 8, a production area in the Primary Building with many tasks, processes and materials, was selected. (See Supporting Information S1: Tables S3 and S4).

2.4 | Mortality and cancer incidence

Vital status and causes of death were updated through 2014 using the Service to Epidemiological Researchers to Provide Vital Status Data on Subjects of Health Research (https://www.ssa.gov/policy/about/epidemiology.html) and linkage with the National Death Index (https://www.cdc.gov/nchs/ndi/index.htm). The underlying cause of death was ascertained from NDI through 2014 and coded to the International Classification of Diseases (ICD) version in effect at the time of death. Cancer incidence was determined by linkage to four state cancer registries: Alabama, Tennessee, Georgia, and Florida. We estimated approximately 90% of the cohort is covered by these four states based on the state of death from mortality records. The remaining states each accounted for less than 1% of deaths. The logistics of obtaining approval for registry linkage for these low-yield states obviated their inclusion. We worked with cancer registry personnel to obtain state-specific approvals for data use and sharing protocols that preserved confidentiality. In compliance with these protocols, cells with fewer than 10 cancer cases identified through the registries are suppressed. The primary cancer diagnosis recorded in the registry was coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) was used for the analysis. The initial outcomes of specific interest were based on prevailing toxicological and epidemiological literature and included cancer of the urinary bladder, kidney, prostate, liver, testes, and pancreas, and diseases of the circulatory system, particularly cerebrovascular disease. Given the extensive interest in the effects of PFAS and the unique nature of this occupationally exposed population we present results for outcomes with a sufficient number of events for the mortality analysis ($N = 3$) and internal analysis with cancer incidence ($N = 10$).

2.5 | Analysis

The all-cause and cause-specific mortality experience of the Decatur cohort was compared to that of the general population of the United States. Our previous mortality analysis[10] had low standardized mortality ratios (SMRs) when using the population of Alabama as a referent. We

chose to use a national referent population to reduce the potential bias from 3M employees, a stably employed population with solid health care benefits, having better than average health outcomes in Alabama. We estimated all-cause and cause-specific SMRs, standardized by age, sex, 5-year age group, and 5-year calendar period, with 95% confidence intervals (CIs) using the National Institute for Occupational Safety and Health (NIOSH) Life Table Analysis System (LTAS).[18] The ICD codes were mapped to cause of death categories developed by NIOSH for the LTAS system. Exposure-specific SMRs were estimated for exposure quartiles of the cumulative PFOS-equivalent exposure (mg/m^3-days) of the decedents in the analyzed population (full cohort and subcohort). The exposure-specific SMRs are based on the age, sex, and calendar period person-time distribution of the cohort members in those exposure quartiles, and thus the SMRs are not comparable between exposure quartiles.

To evaluate risk within the cohort, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using a time-dependent Cox model. Attained age was the time scale beginning at the age of first employment until the end of follow-up or death and time-varying cumulative PFOS-equivalent exposure as an independent variable. The HRs were further adjusted for year of birth and sex. The cumulative PFOS-equivalent exposure was highly skewed (Supporting Information S1: Figure S2). The data were $\log_2$-transformed to normalize the exposure distribution for the analysis on a continuous scale. HRs from the $\log_2$ models can be interpreted as the change in risk associated with a doubling of cumulative exposure. HRs for exposure quartiles were estimates using the same exposure quartiles for the SMR analysis. The models were repeated with the cumulative exposure lagged by 10 and 20 years.

The cancer incidence analysis was restricted to cohort members who survived until 1995 when all four cancer registries were fully established. The cancer incidence analysis included 3899 cohort members who ever worked at the plant and survived until 1995, with 2551 members who had worked at least 365 days. The analysis focused on the following cancers: bladder, lung, kidney, breast, colorectal, pancreatic, prostate, hematopoietic/lymphopoietic, and malignant skin neoplasms, which accounted for 83% of all cancers diagnosed. Though testicular and liver cancer were of interest, only four liver cancers and one testicular cancer were identified, which precluded an exposure-response analysis. Cancer-specific HRs and 95% CIs were estimated with time-dependent Cox models from 1995 until cancer diagnosis, death, or end of follow-up, with attained age as the time scale and the $\log_2$-transformed continuous cumulative exposure, adjusting for age, sex, and year of birth. Exposure categories were based on quartiles of the cumulative PFOS-equivalent exposure (mg/m^3-days) of all cancer cases in the population being analyzed (full cohort and subcohort). The models for cancer incidence were repeated with exposures lagged 10 and 20 years.

Limited data on smoking history were available. A prior health survey[14,15] obtained self-reported smoking history from 1400 respondents and smoking history was ascertained, albeit inconsistently, through occupational health surveillance activities. These sources were merged to classify cohort members as ever/never/missing smokers (Supporting Information S1: Table S9). The models for mortality and cancer incidence within the cohort were analyzed with ever/never history of smoking included as a covariate; first as a complete case analysis then using multiple imputation to account for the missing smoking history. Fully conditional specification,[19] based on age, year of birth, sex, and cumulative exposure generated ten imputed data sets. These imputations were built with the SAS software routine Proc MI and combined in Cox regression models using Proc MIANALYZE to estimate summary HRs and confidence intervals.[20]

3 | RESULTS

A total of 635 and 474 deaths were identified in the full cohort ($N = 4045$) and in the subcohort (worked 365 days or more, $N = 2659$), respectively. Among the cohort members who survived until 1995 (full cohort $N = 3899$ and subcohort $N = 2551$), we identified 451 incident cancers in the full cohort and 338 incident cancers in the subcohort (Table 1). The cohort was mostly male (80%), with an average year of birth of 1953.

The overall death rate was lower than the US population with identical all-cause SMRs for the full cohort and the subcohort (Table 2). The only SMRs for the subcohort above unity were for bladder cancer (SMR = 1.79, 95% CI = 0.72–3.68), cerebrovascular disease (SMR = 1.27, 95% CI = 0.83–1.86) and conduction disorders

TABLE 1 Characteristics of all Decatur cohort members and those with at least 365 days of employment and those alive at the beginning of the cancer incidence follow-up.

	Mortality		Cancer incidence	
Full cohort (all workers)	***N***	**%**	***N***	**%**
Total	4045		3899	
Male	3254	80.4	3116	79.9
Female	791	19.6	783	20.1
Deaths/Cancers	635	15.7	451	11.6
	Mean	**SD**	**Mean**	**SD**
Year of birth	1953	12.4	1953	12.1
Age at first employment (years)	25.4	8.1	25.8	8.0
Age at last follow-up (years)	61.1	12.4	60.6	12.1
Duration of employment (years)	10.4	12.6	10.4	12.7
Subcohort (worked ≥ 365 days)	***N***	**%**	***N***	**%**
Total	2659		2551	
Male	2189	82.3	2087	81.8
Female	470	17.7	464	18.2
Deaths/Cancers	474	17.8	338	13.3
	Mean	**SD**	**Mean**	**SD**
Year of birth	1951	12.7	1952	12.5
Age at first employment (years)	27.0	8.3	27.3	8.2
Age at last follow-up (years)	62.8	12.7	62.2	12.5
Duration of employment (years)	15.7	12.8	15.7	12.8

TABLE 2 Standardized mortality ratios (SMR) by PFOS exposure equivalents (mg/m^3-days) quartile for members of the Decatur plant cohort.

	Total			Exposure quartiles[a]											
				Q1			Q2			Q3			Q4		
Cause	*N*	SMR	(95% CI)	*N*	SMR	(95% CI)	*N*	SMR	(95% CI)	*N*	SMR	(95% CI)	*N*	SMR	(95% CI)
Full cohort (all workers)															
All causes	635	0.81	(0.74–0.87)	159	0.68	(0.58–0.80)	158	0.77	(0.66–0.90)	159	0.89	(0.76–1.04)	159	0.92	(0.78–1.08)
All cancers	172	0.79	(0.68–0.92)	47	0.82	(0.60–1.09)	43	0.72	(0.52–0.97)	36	0.72	(0.51–1.00)	46	0.92	(0.67–1.22)
Pancreatic cancer	9	0.71	(0.33–1.35)	3	0.88	(0.18–2.58)	2	0.57	(0.07–2.06)	1	0.36	(0.01–1.98)	3	1.03	(0.21–3.01)
Prostate cancer	3	0.32	(0.07–0.93)	1	0.58	(0.01–3.22)	1	0.41	(0.01–2.29)	0	0.00	(0.00–1.52)	1	0.35	(0.01–1.97)
Kidney cancer	3	0.46	(0.10–1.35)	1	0.56	(0.01–3.14)	0	0.00	(0.00–2.08)	2	1.40	(0.17–5.05)	0	0.00	(0.00–2.44)
Bladder	7	1.42	(0.57–2.92)	1	0.88	(0.02–4.93)	1	0.75	(0.02–4.16)	1	0.86	(0.02–4.77)	4	3.06	(0.83–7.83)
Lung cancer	71	1.03	(0.81–1.30)	16	0.96	(0.55–1.56)	20	1.05	(0.64–1.61)	14	0.88	(0.48–1.47)	21	1.23	(0.76–1.88)
Liver cancer	6	0.68	(0.25–1.48)	2	0.73	(0.09–2.64)	2	0.85	(0.10–3.05)	2	1.09	(0.13–3.93)	0	0.00	(0.00–1.94)
Colon cancer	4	0.26	(0.07–0.66)	1	0.25	(0.01–1.39)	1	0.24	(0.01–1.32)	1	0.28	(0.01–1.54)	1	0.27	(0.01–1.50)
Hemopoietic/Lymphopoietic	21	0.94	(0.58–1.44)	6	0.97	(0.36–2.11)	5	0.84	(0.27–1.96)	4	0.79	(0.21–2.01)	6	1.19	(0.44–2.59)
Ischemic heart disease	89	0.61	(0.49–0.75)	27	0.76	(0.50–1.10)	17	0.45	(0.26–0.72)	22	0.63	(0.39–0.95)	23	0.63	(0.40–0.94)
Cerebrovascular disease	32	1.22	(0.83–1.72)	6	0.94	(0.35–2.05)	7	1.01	(0.40–2.07)	7	1.08	(0.43–2.22)	12	1.87	(0.96–3.26)
Conduction disorder	33	3.03	(2.09–4.26)	4	1.40	(0.38–3.57)	11	3.83	(1.91–6.85)	10	3.93	(1.88–7.23)	8	3.09	(1.33–6.09)
Subcohort (worked ≥ 365 days)															
All causes	474	0.81	(0.73–0.88)	118	0.68	(0.56–0.81)	119	0.77	(0.64–0.93)	119	0.93	(0.77–1.12)	118	0.89	(0.74–1.07)
All cancers	128	0.77	(0.64–0.91)	37	0.79	(0.56–1.09)	26	0.57	(0.37–0.84)	28	0.78	(0.52–1.13)	37	0.95	(0.67–1.32)
Pancreatic cancer	7	0.73	(0.29–1.50)	2	0.75	(0.09–2.70)	2	0.75	(0.09–2.70)	0	0.00	(0.00–1.82)	3	1.33	(0.27–3.89)
Prostate cancer	3	0.39	(0.08–1.13)	2	1.09	(0.13–3.96)	0	0.00	(0.00–2.06)	1	0.52	(0.01–2.92)	0	0.00	(0.00–1.66)
Kidney cancer	2	0.41	(0.05–1.46)	0	0.00	(0.00–2.62)	1	0.75	(0.02–4.20)	1	0.97	(0.02–5.42)	0	0.00	(0.00–3.14)
Bladder	7	1.79	(0.72–3.68)	2	1.97	(0.24–7.11)	0	0.00	(0.00–3.67)	1	1.15	(0.03–6.38)	4	3.91	(1.07–10.02)
Lung cancer	51	0.95	(0.70–1.24)	12	0.82	(0.42–1.44)	12	0.83	(0.43–1.46)	11	0.94	(0.47–1.68)	16	1.21	(0.69–1.97)
Liver cancer	3	0.46	(0.10–1.36)	1	0.54	(0.01–3.00)	1	0.55	(0.01–3.06)	1	0.77	(0.02–4.29)	0	0.00	(0.00–2.49)
Colon cancer	3	0.25	(0.05–0.73)	0	0.25	(0.00–1.11)	1	0.32	(0.01–1.76)	1	0.38	(0.01–2.10)	1	0.35	(0.01–1.94)
Hemopoietic/Lymphopoietic	15	0.88	(0.49–1.46)	6	1.21	(0.44–2.63)	2	0.45	(0.05–1.61)	2	0.55	(0.07–1.99)	5	1.29	(0.42–3.00)
Ischemic heart disease	68	0.60	(0.47–0.76)	20	0.65	(0.40–1.00)	17	0.61	(0.36–0.98)	14	0.53	(0.29–0.90)	17	0.60	(0.35–0.96)
Cerebrovascular disease	26	1.27	(0.83–1.86)	4	0.73	(0.20–1.88)	6	1.14	(0.42–2.48)	4	0.83	(0.23–2.13)	12	2.42	(1.25–4.22)
Conduction disorder	28	3.36	(2.23–4.86)	7	2.99	(1.20–6.16)	8	3.77	(1.63–7.43)	7	3.77	(1.52–7.76)	6	2.99	(1.10–6.50)

[a]Quartile cut-points: All workers 0.28, 28.99, 435.55 PFOS exposure equivalents mg/m^3-days; Worked ≥ 365 days 1.15, 127.09, 710.03 PFOS exposure equivalents mg/m^3-days. Quartiles based on exposure distribution of deceased in the cohort.

(SMR = 3.36, 95% CI = 2.23–4.86), with similar results for the entire cohort. The exposure-specific SMRs for bladder cancer were elevated in Q4 for the whole cohort (3.06, 95% CI = 0.83–7.83), and for Q1 and Q4, (1.97, 95% CI = 0.24–7.11 and 3.91, 95% CI = 1.07–10.02), respectively in the subcohort. The SMR for cerebrovascular disease was elevated in Q4 of the subcohort (2.42, 95% CI = 1.25–4.22), and the SMRs for conduction disorders were elevated across the exposure ranges.

The mortality analysis within the cohort by continuous cumulative exposure provided limited evidence of potential associations (Table 3). While the HRs for bladder cancer, lung cancer, and cerebrovascular disease showed a positive association, the estimates were statistically imprecise. When cumulative exposure was lagged 10- and 20-years, slight increases were revealed in the point estimates for bladder cancer. Results by exposure quartile (Supporting Information S1: Tables S5 and S6) revealed similar patterns with elevated HRs for the highest exposure quartile for bladder and lung cancer and cerebrovascular disease, but the confidence intervals were wide and included 1.

The registry linkage identified the following cancers in the full cohort (subcohort in parentheses), 26 (22) bladder, 18 (13) kidney, 140 (108) prostate, 19 (11) breast, 11 (10) pancreatic, 36 (26) colorectal, 69 (54) lung, 22 (16) hematopoietic/lymphopoietic, and 42 (27) malignant neoplasms of the skin (Table 4). The nonlagged point estimates for $\log_2$ cumulative PFOS-equivalent exposure offered little evidence of an association with all cancers except lung cancer which showed a rate increase of 4% (HR = 1.04, 95% CI = 1.00–1.09) and 5% (HR = 1.05, 95% CI = 1.00–1.11) with each doubling of cumulative exposure in the full and subcohorts, respectively, and for colorectal cancer in the subcohort (HR = 1.08, 95% CI = 0.99–1.17) (Table 4). When the exposures were lagged 10 and 20 years, the association between PFOS-equivalent exposure and bladder and pancreatic cancer incidence increased (Table 4). The association between cumulative exposure and lung cancer changed little on the continuous scale, but the HR for the fourth exposure quartile did increase in both populations when the exposure was lagged (0, 10, and 20 years): HR = 1.83 (95% CI = 0.88–3.81), HR = 2.08 (95% CI = 0.95–4.55), HR = 2.32 (95% CI = 1.06–5.06) for the whole cohort and HR = 1.98 (95% CI = 0.88–4.46), HR = 1.99 (95% CI = 0.88–4.47), and HR = 2.39 (95% CI = 1.01–5.65) for the subcohort, respectively (Supporting Information S1: Tables S7 and S8). For colorectal cancer the HRs on the continuous scale decreased with lagged exposures, but the HR for the fourth quartile lagged 20 years was elevated (HR = 3.27, 95% CI = 1.05–10.16) for the subcohort (Supporting Information S1: Table S8). In these analyses by exposure category, all cancers except lung and prostate had few cases, thus the results are statistically difficult to interpret.

Smoking information was missing for 41.3% of the whole cohort and 18.1% of the subcohort (Supporting Information S1: Table S9). Within the population with data on smoking, the prevalence of ever smoking was positively associated with exposure. A larger proportion of the lower exposure quartile in the full cohort had missing smoking data. This is likely due to the greater number of short-term workers in this quartile who would be less likely to undergo medical surveillance examinations and were not eligible for the mailed survey. The smoking-adjusted effect estimates for lung mortality and bladder and lung cancer incidence were minimally attenuated (Table 5 and Supporting Information S1: Tables S10–S13), suggesting some

TABLE 3 Hazard Ratios for selected causes of death associated with $\log_2$ PFOS exposure equivalents (mg/m^3-days) for members of the Decatur Plant cohort with 0-, 10-, and 20-year exposure lag periods.

	No lag			10-year lag		20-year lag	
Cause of death	N	HR[a,b]	95% CI	HR[a,b]	95% CI	HR[a,b]	95% CI
Full cohort (All workers)							
Bladder cancer	7	1.07	0.90–1.27	1.08	0.92–1.26	1.09	0.97–1.24
Lung cancer	71	1.01	0.97–1.06	1.02	0.98–1.06	1.01	0.98–1.04
Cerebrovascular disease	32	1.03	0.97–1.10	1.02	0.96–1.07	1.01	0.97–1.06
Conduction disorder	33	1.05	0.99–1.11	1.05	0.99–1.11	1.05	1.00–1.10
Ischemic heart disease	89	1.01	0.97–1.05	1.02	0.99–1.05	1.01	0.99–1.04
Subcohort (worked ≥ 365 days)							
Bladder cancer	7	1.03	0.87–1.23	1.05	0.90–1.22	1.08	0.96–1.21
Lung cancer	51	1.03	0.97–1.09	1.03	0.99–1.09	1.01	0.97–1.04
Cerebrovascular disease	26	1.06	0.97–1.15	1.01	0.95–1.09	1.00	0.94–1.05
Conduction disorder	28	1.01	0.94–1.09	1.02	0.96–1.09	1.03	0.97–1.08
Ischemic heart disease	68	1.00	0.95–1.05	1.02	0.98–1.06	1.02	0.98–1.05

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]HR associated with a 1-unit increase in $\log_2$-transformed cumulative PFOS exposure equivalents (mg/m^3-days).

[b]HR adjusted for age, year of birth, and sex.

TABLE 4 Hazard ratios for selected cancer diagnoses associated with $\log_2$ PFOS exposure equivalents (mg/m^3-days) for members of the Decatur Plant cohort with 0-, 10-, and 20-year exposure lag periods.

	No lag			10-year lag		20-year lag	
Cancer diagnosis	*N*	HR[a,b]	95% CI	HR[a,b]	95% CI	HR[a,b]	95% CI
Full cohort (all workers)							
Bladder	26	1.03	0.97–1.10	1.04	0.98– 1.11	1.06	1.00–1.12
Lung	69	1.04	1.00–1.09	1.03	0.99–1.08	1.04	1.00–1.08
Kidney	18	1.01	0.93–1.09	1.02	0.95–1.09	1.02	0.95–1.08
Breast	19	1.04	0.96–1.14	0.98	0.92–1.04	0.98	0.93–1.03
Colorectal	36	1.03	0.97–1.09	1.02	0.97–1.07	1.01	0.97–1.06
Pancreatic	11	1.07	0.96–1.19	1.08	0.97–1.20	1.10	0.99–1.22
Prostate	140	1.01	0.98–1.04	1.00	0.98–1.03	1.01	0.99–1.03
Hematopoietic/Lymphopoietic	22	1.02	0.95–1.09	1.03	0.97–1.10	1.00	0.95–1.06
Other malignant skin neoplasms	42	1.00	0.95–1.05	1.01	0.96–1.05	1.01	0.97–1.06
Subcohort (worked ≥ 365 days)							
Bladder	22	1.02	0.93–1.10	1.03	0.96–1.11	1.05	0.98–1.12
Lung	54	1.05	1.00–1.11	1.04	0.99–1.09	1.04	1.00–1.09
Kidney	13	0.98	0.88–1.09	1.00	0.92–1.08	1.00	0.94–1.08
Breast	11	0.98	0.86–1.12	0.95	0.90–1.01	0.97	0.92–1.03
Colorectal	26	1.08	0.99–1.17	1.04	0.98–1.12	1.03	0.98–1.08
Pancreatic	10	1.05	0.93–1.19	1.06	0.95–1.19	1.09	0.97–1.22
Prostate	108	1.01	0.97–1.04	1.00	0.97–1.03	1.01	0.99–1.04
Hematopoietic/Lymphopoietic	16	1.00	0.90–1.10	1.01	0.93–1.10	0.98	0.93–1.04
Other malignant skin neoplasms	27	1.04	0.96–1.12	1.02	0.96–1.08	1.02	0.97–1.08

[a]HR associated with a 1-unit increase in $\log_2$-transformed cumulative PFOS exposure equivalents (mg/m^3-days).
[b]HR adjusted for age, year of birth, and sex (except breast and prostate cancer which are restricted by sex).

potential confounding by smoking history. Nevertheless, the positive associations remained. Complete case analyses were conducted, and the overall results (not shown) were consistent with both the unadjusted models and the models adjusting for smoking with imputed missing values.

4 | DISCUSSION

While overall death rates from all causes and all cancers were lower than expected, we observed some evidence of an association between POSF-based exposure and death from bladder cancer and cerebrovascular disease. Within the cohort, we observed associations with incidence of bladder, lung, colorectal, and pancreatic cancer. However, except for lung cancer, the precision of these estimates could not preclude a chance finding. Lagging the exposures by 10 and 20 years modestly increased the HRs for bladder and lung cancers. Adjusting for smoking using limited data attenuated the HRs for bladder, lung, and pancreatic cancers but did not substantially alter the interpretation.

Compared to the previous mortality study of this cohort,[10] our updated analysis of this cohort benefitted from an additional 15 years of follow-up, the inclusion of cancer incidence data from state cancer registries, and an updated exposure model that more accurately reflected individual cohort members' exposure. Several limitations must also be considered when interpreting these data, including a small number of events for some outcomes of interest, which limited the statistical power of the study, limited information on smoking and other confounders, and potential under-ascertainment of cancers particularly due to left truncation of incident cancer ascertainment which was only available from 1995. Additionally, this stable workforce which enjoys good health care benefits may experience better health outcomes than the general population of the United States, the referent population for the mortality analysis. The possibility that a healthy worker effect biased the SMRs to the null cannot be ruled out.

The increased risk of bladder cancer was previously observed in a mortality study, based on only three cases,[10] and the subsequent study that included a case finding exercise to identify nonfatal cancers as well for a total of eleven cases.[14] The current mortality results include four additional bladder cancer deaths in a larger

TABLE 5 Hazard ratios for selected causes of death and incident cancers associated with $\log_2$ PFOS exposure equivalents (mg/m^3-days) for members of the Decatur Plant cohort with 0-, 10-, and 20-year exposure lag periods, adjusted for smoking with missing smoking data imputed.

	No lag			10-year lag		20-year lag	
	N	HR[a,b]	95% CI	HR[a,b]	95% CI	HR[a,b]	95% CI
Mortality							
Full cohort (All workers)							
Bladder cancer	7	1.08	0.91–1.29	1.09	0.92–1.29	1.10	0.97–1.25
Lung cancer	71	1.01	0.97–1.05	1.01	0.98–1.05	1.00	0.97–1.03
Cerebrovascular disease	32	1.03	0.97–1.11	1.02	0.96–1.08	1.01	0.97–1.06
Subcohort (Worked ≥ 365 days)							
Bladder cancer	7	1.05	0.88–1.25	1.06	0.90–1.24	1.08	0.96–1.23
Lung cancer	51	1.02	0.96–1.08	1.03	0.98–1.08	1.00	0.97–1.04
Cerebrovascular disease	26	1.06	0.97–1.16	1.01	0.95–1.09	1.00	0.94–1.05
Cancer Incidence							
Full cohort (All workers)							
Bladder	26	1.03	0.96–1.10	1.04	0.98–1.10	1.05	0.99–1.12
Lung	69	1.03	0.99–1.08	1.03	0.99–1.07	1.03	1.00–1.07
Colorectal	36	1.03	0.97–1.09	1.02	0.97–1.07	1.01	0.97–1.06
Kidney	18	1.01	0.93–1.09	1.02	0.95–1.09	1.02	0.96–1.08
Pancreatic	11	1.07	0.96–1.19	1.07	0.97–1.19	1.09	0.99–1.21
Prostate	140	1.01	0.98–1.04	1.00	0.98–1.03	1.01	0.99–1.03
Subcohort (Worked ≥ 365 days)							
Bladder	22	1.01	0.93–1.10	1.02	0.95–1.10	1.05	0.98–1.12
Lung	54	1.04	0.99–1.10	1.03	0.98–1.08	1.04	0.99–1.08
Colorectal	26	1.08	0.99–1.17	1.04	0.98–1.12	1.03	0.98–1.08
Kidney	13	0.98	0.88–1.09	1.00	0.92–1.09	1.00	0.94–1.08
Pancreatic	10	1.05	0.92–1.19	1.06	0.94–1.19	1.09	0.97–1.22
Prostate	108	1.01	0.97–1.04	1.00	0.97–1.03	1.01	0.99–1.04

[a]HR associated with a 1-unit increase in $\log_2$-transformed cumulative PFOS exposure equivalents (mg/m^3-days).
[b]HR adjusted for age, year of birth, smoking history (yes/no), sex.

cohort and suggests some attenuation of the original finding. The analysis of incident cancers from 1995 onward showed limited evidence of an association between POSF-based exposure and bladder cancer. An analysis of cancer incidence and community drinking water exposure to primarily PFOS and PFHxS in Ronneby, Sweden found a positive, but imprecise association with bladder cancer incidence when comparing the highest to lowest exposures (HR = 1.50, 95% CI = 0.98–2.29).[21] This ecologic study had the advantage of a large population (N = 60,507) and fairly complete case ascertainment, but lacked data on individual exposure and confounding factors. Studies of Sprague–Dawley rats that were exposed to dietary K-PFOS[22] and POSF via inhalation[23] showed no evidence of bladder neoplasm formation.

We observed an association between POSF-based exposure and lung cancer that was not fully explained by the information available on smoking. Studies of occupational populations and the majority of studies of exposed communities that evaluated lung cancer have not reported lung cancer and PFOS or other PFAS exposure associations.[9,10,24–28] The community exposure study in Ronneby, Sweden, reported a weakly positive association comparing the highest to lowest exposure group (HR = 1.32, 95% CI = 0.92–1.88). They also reported a standardized incidence ratio (SIR) of 1.42 (95% CI = 1.09–1.81) in exposed men. However, the SIR was also somewhat elevated for nonexposed men (SIR = 1.11, 95% 0.96–1.29), and there was no evidence of an increased risk in women.[21] An important distinction of our study cohort is that inhalation was the primary POSF exposure route in this occupational setting in contrast to exposure through contaminated drinking water. The 13-week study of Sprague–Dawley rats exposed to high levels of POSF via inhalation showed evidence of damage to the respiratory

tract tissues.[23] This effect was attributed to the release of hydrogen fluoride (HF) during hydrolysis of POSF to PFOS. HF is highly corrosive and acute inhalation exposures will cause inflammation, ulceration, and even death. However, it has not been shown to be carcinogenic.[29] The exposures to the members of this cohort were relatively low and unlikely to cause direct effects on respiratory tissue.

The observed associations between POSF-based exposure and bladder and lung cancers could be due to confounding by smoking, though this was not evident after adjusting to our limited smoking data. Smoking history was positively associated with cumulative exposure, but the data were incomplete. Moreover, with data on smoking being limited to ever/never, we were unable to characterize important factors like the intensity and duration of smoking, thus limiting the extent to which confounding could be controlled. The techniques we used for accounting for missing data are well-known but require important assumptions.[30–32] Using complete case or multiple imputation methods lean on the assumption that the data are, at least to a reasonable degree, missing at random. The sources of our data could result in missing data being more common in individuals with less work experience, thus limiting the validity of these imputed models.

Evidence for exposure related associations with other cancers in this study was weak to nonexistent. We did observe a positive association with pancreatic cancer, but the number of total cases resulted in statistically unstable estimates. Pancreatic cancer has not been observed in other studies of PFOS or PFOA exposed populations. An association with incident colorectal cancer was observed in cohort members with at least 365 days of employment. There were only, three deaths from colon cancer (SMR = 0.25, 95% CI = 0.05–0.73) and two deaths from rectal cancer (SMR = 0.65, 95% CI = 0.08–2.36) in the subcohort. The extent to which screening practices contributed to this dichotomy is unknown. A community-based PFOS exposure study[33] where exposures were orders of magnitude lower than exposures in this cohort reported an inverse association with colorectal cancer. Other research has reported associations between PFOS exposure and prostate[34] and breast cancer[35] in nonoccupational exposed populations, but we observed little evidence to support these associations.

While our study did not report an association with kidney cancer and total PFOS equivalents, it should be noted that Steenland and Woskie[9] reported an association with kidney cancer mortality and PFOA exposure, which was not observed in another occupational cohort study of PFOA that used the same exposure matrix methodology as the present study.[26] A nested case–control study from the PLCO screening trial reported a PFAS association with kidney cancer, which was primarily attributed to PFOA,[36] but it is notable that the range of exposure for the PLCO cohort is similar to the general population without an identifiable exposure source and orders of magnitude lower than this occupationally exposed population. The Ronneby community cohort did report an increased risk of kidney cancer in the highest exposed category.[21]

Purdue et al. observed an association with testicular germ cell tumors and serum PFOS in US Air Force service men.[37] We observed only one case of testicular cancer, however the cohort had an average age of 44 years when cancer incidence follow-up began and the age of onset for testicular cancer is predominantly younger with approximately 75%–80% of cases diagnosed below this age (https://seer.cancer.gov/statfacts/html/testis.html). It is plausible other cases were diagnosed before the registries were operational, thus we cannot not fully assess the risk of testicular cancer in this cohort. Barry, et al., reported an association with testicular cancer in the highest quartile of a population with both community and occupational exposed to PFOA.[24] Evidence of testicular cancer as an endpoint of concern was not supported based on a 2-year bioassay of Sprague–Dawley rats.[38]

Under-ascertainment of cancers through the registry linkage is a potential limitation of this study. The registry linkage included four state cancer registries which, based on state of death from the mortality data, likely captured over ninety percent of the cancer cases. The cases not captured, i.e., the cohort member is not living in those states when the cancer was diagnosed, may be differentially distributed by exposure, thus biasing the estimates. The extent to which this under ascertainment is related to exposure is not known. Under-ascertainment of cancers with a younger age of onset, like testicular cancer, or cancers in older workers who worked in the early years of the plant's operation, is a limitation presented by the left-truncation of follow-up as the cancer registries were not fully operational until 1995. Potential selection bias from left-truncation can lead to an attenuation of effects when cohort members who survived cancer free until 1995, thus at risk of developing primary cancer during the abbreviated follow-up and have had the opportunity to accrue more exposure, are less susceptible to the effects of exposure.[39] The most likely effect of this bias is an underestimate of the true effect.

An increased risk of dying from cerebrovascular disease was not observed in our previous analysis. A mortality study of the 3M Cottage Grove facility, which produced PFOA, reported a modest cumulative-exposure-related association with increased risk of dying from cerebrovascular disease within the cohort, but not when compared to the general population.[11] A follow-up to that study did not observe any exposure-associated relationship with cerebrovascular disease in comparison to the general population or to a nonexposed 3M cohort with workers in the same union.[26] Other studies of occupational PFAS exposure have not reported associations with cerebrovascular disease.[25,40] nor was one observed in relation to community exposure from contaminated water in the C8 Health Project population.[41] Pitter, et al. reported a positive association between serum PFOS, and other PFAS, and both systolic and diastolic blood pressure and self-reported hypertension in young adults in a community exposed through drinking water in Northern Italy.[42] The mean serum PFOS concentrations in Pitter, et al. were substantially lower than those estimated for the Decatur cohort, 4.63 ng/mL vs 1.32 ppm (1320 ng/mL)[12] respectively.

The elevated SMRs for cardiac conduction disorders was likely due to death certificate recording practices. Of the 33 conduction disorders deaths, 30 had an underlying cause of 'Cardiac Arrest, Unspecified' (ICD 10 I46,9 and ICD9 427.5). This category can be a catch-all for undetermined causes of death. To investigate, we used Centers for Disease Control and Prevention data[43] to compare Alabama to the US population. The Alabama age-adjusted mortality rate for cardiac arrest unspecified is 37.2/100,000 compared to 5.3/100,000 for the US; a sevenfold excess. By contrast, the rate in Alabama for all circulatory disease mortality is 331.0/100,000 compared to 261.4/100,000 in the entire country; a ratio of 1.3. This suggests the association between conduction disorders and working in the Decatur plant is due to misclassification. Investigators for a cohort study of automotive electronics manufacturing workers in Alabama reached similar conclusions where the SMR for conduction disorder was 3.74 when the US population was the referent and 0.98 when Alabama was the referent.[44]

Compared to earlier analyses of this cohort, we utilized a much more detailed and quantitative exposure model that identified exposure not only by job title, but by task that was specific to the activities of workers in specific roles and accounted for changing practices over time. A limitation of this study was the lack of an external validity assessment to evaluate the task-based job department exposure matrix used to calculate the Total PFOS equivalents in this study.

Respiratory exposure was the main route of exposure and for which there were more comprehensive industrial hygiene monitoring data. Wipe sample data were not used in the exposure assessment since they were only available for a very limited number of years, agents and locations. Because PFOS-related compounds have limited water and lipid solubility, dermal absorption was not expected to be significant compared to airborne exposure potential.[1] Respirator usage was not considered when calculating exposure group concentrations since sufficiently detailed information on respirator usage across all decades was not documented. We did not have sufficient details on the use of respirators going back in time such that bias could result in unknown misclassification (either over or under estimation) for a number of exposure teams. Before the late 1990s, respiratory protection was primarily selected based on exposure potential to nonfluorinated solvents, corrosives, and direct handling of POSF. Many other tasks with exposure potential to study PFAS did not have respirators required. When respirators were used, they were only required during the task, but employees could remain in the production area before vapor concentrations subsided. Applying respiratory protection factors when the documentation and data were unreliable would likely introduce misclassifications resulting in over and under estimation of exposure across multiple groups.

Our exposure model was limited to workplace exposures. It is possible that a small number of the cohort lived in areas with documented PFAS contamination in drinking water in the area.[45] This exposure could result in an attenuation of the observed associations because the impact would be greatest in workers with lower occupational exposure as the exposures in the POSF production areas were substantially higher.

In summary, this study provides some evidence that occupational PFOS exposure is associated with a few specific causes of death or cancer. However, due to the seriousness of the diseases and the size of the point estimates of effects, the possible associations between PFOS exposure and bladder cancer, lung cancer, and cerebrovascular disease warrant further consideration.

AUTHOR CONTRIBUTIONS

Bruce H. Alexander, Andrew Ryan, Timothy R. Church, and Hyun Kim: Conception and design of the study and data acquisition. **Geary W. Olsen and Perry W. Logan**: Design, acquisition of data, and summary of exposure matrix. **Bruce H. Alexander, Andrew Ryan, Timothy R. Church, and Hyun Kim**: Analysis and interpretation of the data, and drafting manuscript. **Bruce H. Alexander, Andrew Ryan, Timothy R. Church, Hyun Kim, Geary W. Olsen, and Perry W. Logan**: Review of manuscript and approval of final version published.

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CONFLICT OF INTEREST STATEMENT

The 3M Company has previously provided financial support to the University of Minnesota School of Public Health to support students and independent research endeavors. Geary Olsen is a current employee and Perry Logan a retired employee of the 3M Company. The other authors declare no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Leena Nylander-French declares that she has no conflict of interest in the review and publication decision regarding this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on a limited basis on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS APPROVAL AND INFORMED CONSENT

The protocol for this study was reviewed and approved by the University of Minnesota Human Subjects Research Committee. Linkage with cancer registries was also approved by the registry-specific institutional review boards.

DISCLAIMER

The findings and conclusions presented in this paper are those of the authors and do not necessarily represent the official position of the Univeristy of Minnesota, the 3M Company, or the contributing cancer registries.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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